Quorum sensing N-Acyl homoserine lactones are a new class of anti-schistosomal

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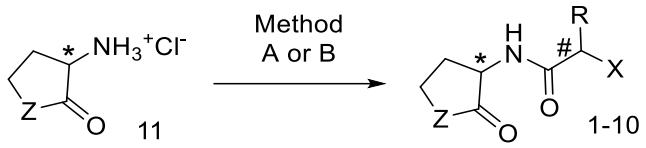
S1 Protocol



Scheme 1: Method A: NEt_3, $CHCl_3$, 0°C; Method B: K_2CO_3, CH_2Cl_2/H_2O, 0°C. R = H. Me, X = O, S.* Chiral centres

Materials and Methods for Chemical synthesis of compounds 1 – 9

All reactions were monitored by thin layer chromatography and visualised by either I_2, UV light or phosphomolybdic acid. Flash chromatography was carried out on Fluorochem Silicagel 60Å (40-63 micron) with eluting solvent as indicated. ^1H and ^{13}C NMR spectroscopy was carried out on a Bruker Ultrashielded Plus 400 MHz spectrometer in $CDCl_3$ unless otherwise stated and are reported in ppm referenced to the solvent internal standard at 7.62 and 77.160 ppm respectively. Infrared spectroscopy was carried out on a Bruker Alpha ATR using solid state compound. Mass spectrum were recorded on either a Finnigan MAT 900 XLT or a Finnigan MAT 95 XP at the EPSRC National Mass Spectrometry Service Centre in Swansea. Optical rotations were determined on an ADP440 Polarimeter.

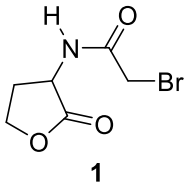
Method A (Used for compounds **1, 2, 7** and **9**)

The acyl halide (1.00-2.65 equiv.) was added in a dropwise manner over 5 min to a stirred and cooled (0°C) solution of the aminolactone salt (1 equiv.) and triethylamine (2 equiv.) dissolved in chloroform. After 2 h the reaction was warmed to rt and stirred for 16 h. After evaporation, the mixture was triturated with EtOAc (3 x 10 mL), filtered, evaporated and purified via column chromatography.

Method B (Used for compounds **3, 4, 5, 6** and **8**)

The acyl halide (1.00-2.65 equiv.) was added in a dropwise manner over 5 min to a stirred and cooled (0°C) solution of the aminolactone salt (1 equiv.) and potassium carbonate (3. equiv.) dissolved in a mixture of chloroform and water. After 2 h the reaction was warmed to rt and stirred for 16 h whereupon the organic layer was separated, and the aqueous phase extracted with chloroform (20 mL). The combined organic layers were washed with tartaric acid solution (5% aq., 2 x 5 mL) and water (2 x 5 mL), dried over $MgSO_4$, evaporated, and purified by column chromatography.

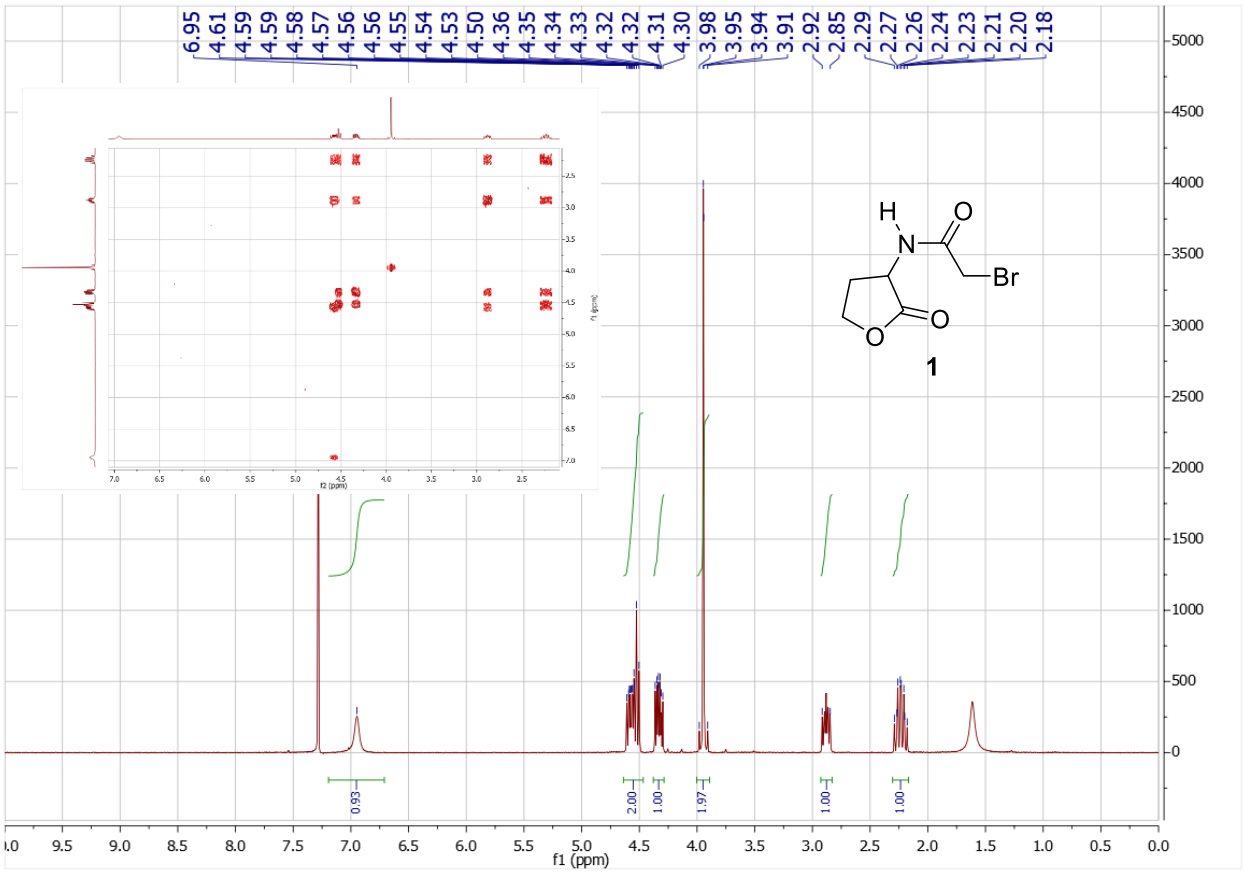
Compound 1: 2-bromo-N-(2-oxotetrahydrofuran-3-yl)acetamide 1[1]

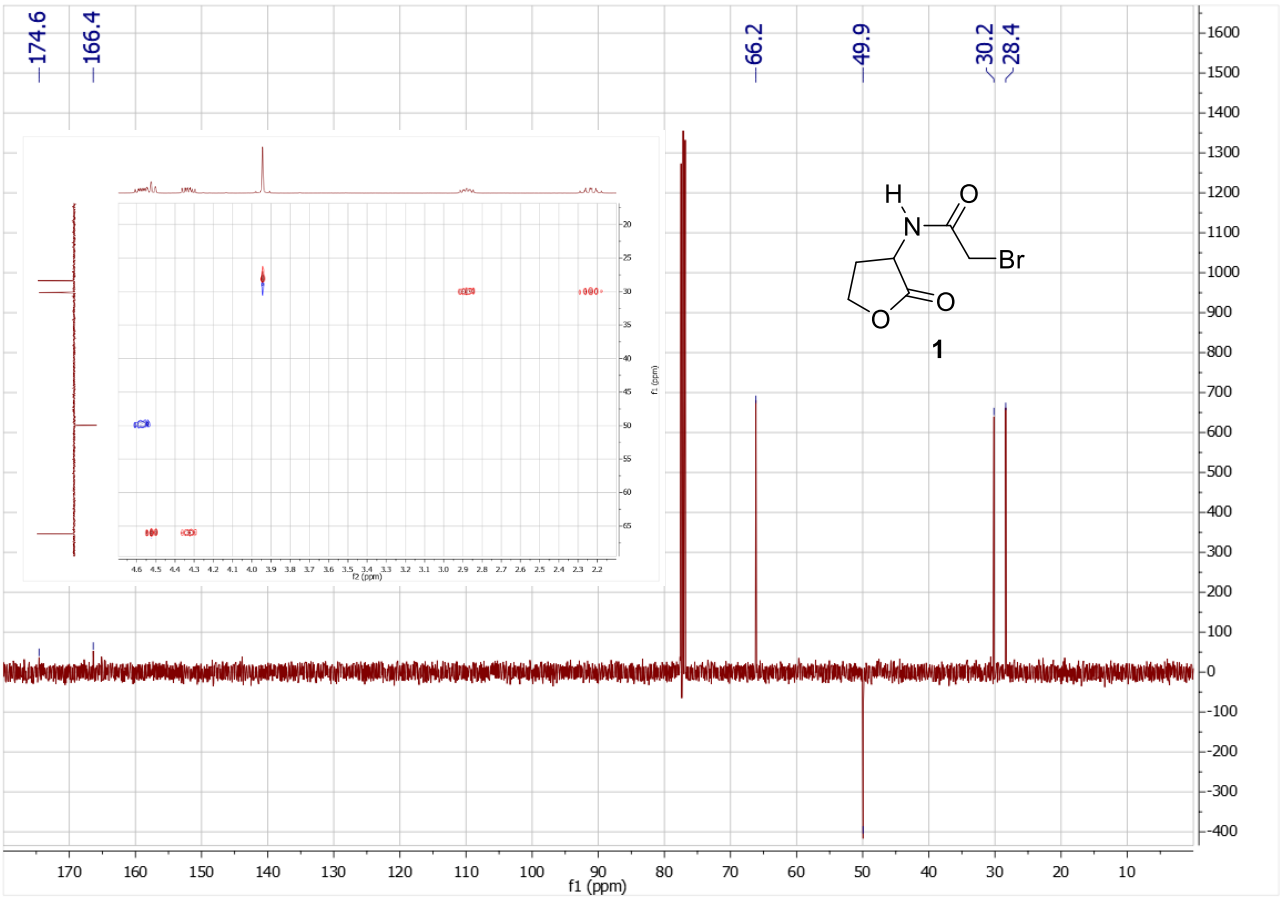


1

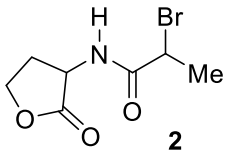
2-bromo-*N*-(2-oxotetrahydrofuran-3-yl)acetamide
Chemical Formula: $C_6H_8BrNO_3$
Exact Mass: 220.9688
Molecular Weight: 222.0380

Bromoacetyl bromide (1.47 g, 7.27 mmol, 0.63 mL), α-amino-γ-butyrolactone hydrobromide (500 mg, 2.75 mmol), triethylamine (556 mg, 5.49 mmol), in chloroform (20 mL). Column chromatography (50% EtOAc in chloroform) gave **1** (612 mg, 2.76 mmol) in 75% yield as a white solid. δ_H 6.95 (1H, br s, NH), 4.56 (1H, ddd, *J* 6.1, 8.6, 11.5 Hz, CH), 4.52 (1H, br t, *J* 8.9 Hz, CH), 4.33 (1H, ddd, *J* 5.9, 9.5, 11.1 Hz), 3.96 (1H, d, *J* 14.0 Hz, CH), 3.92 (1H, d, *J* 14.0 Hz, CH), 2.84-2.92 (1H, m, CH), 2.18-2.29 (1H, m, 1H) ; δ_C 174.6, 166.4, 66.2, 50.0, 30.1, 28.4; ν_{max} 3250, 3062, 1760, 1659, 1548, 1180; MS(CI) 222.0 (100%, $[C_6H_8{}^{79}BrNO_3+H]^+$) 224.0 (98%, $[C_6H_8{}^{81}BrNO_3+H]^+$), 244.0 (85%, $[C_6H_8{}^{79}BrNO_3+Na]^+$), 246.0 (85%, $[C_6H_8{}^{79}BrNO_3+Na]^+$); HRMS(ES) found 221.9762, $C_6H_9{}^{79}BrNO_3{}^+$ ($[M+H]^+$) requires 221.9760; Microanalysis: found C 32.6, H 3.8, N 6.4, Br 36.0; $C_6H_8BrNO_3$ requires C 32.4, H 3.6, N 6.3, Br 36.0.



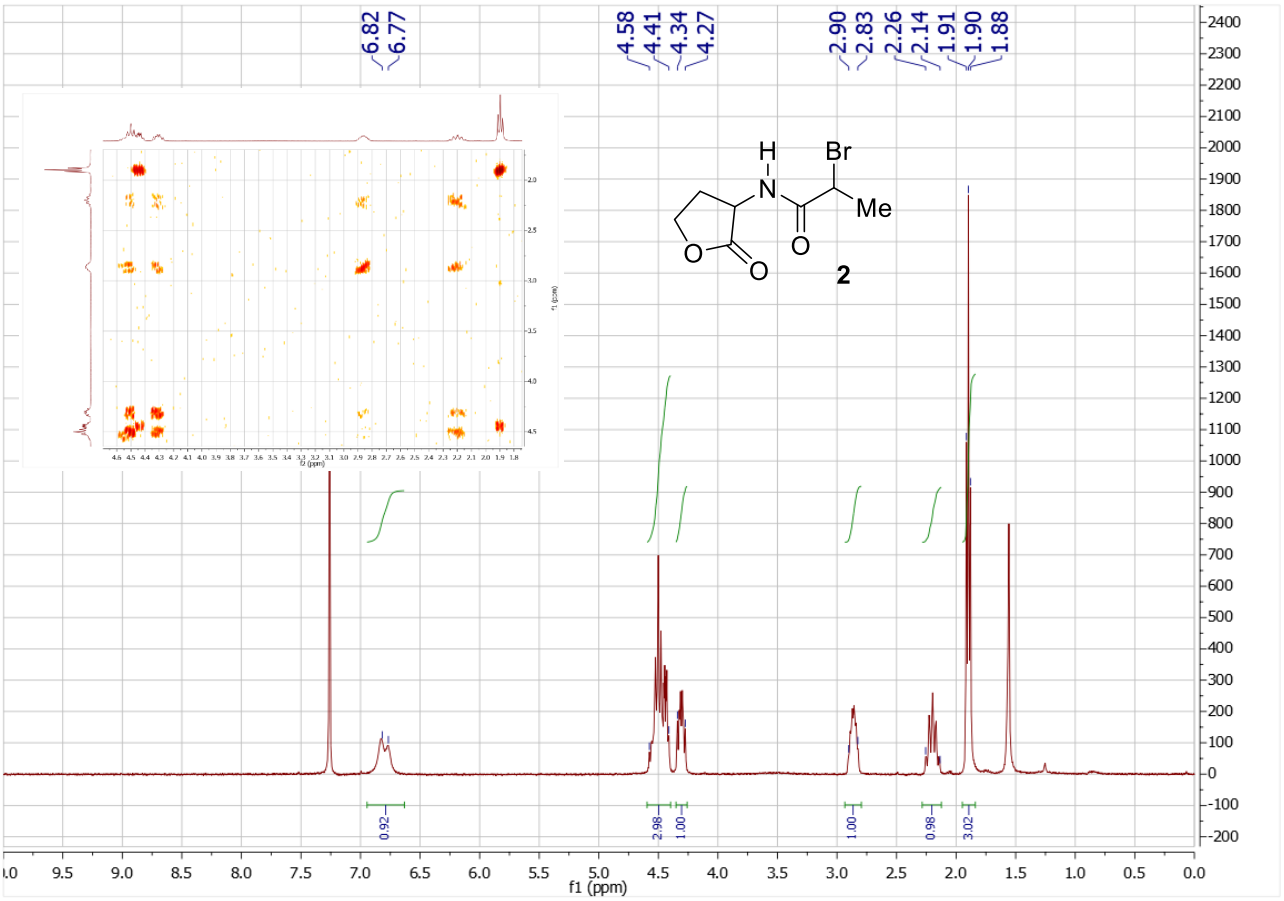


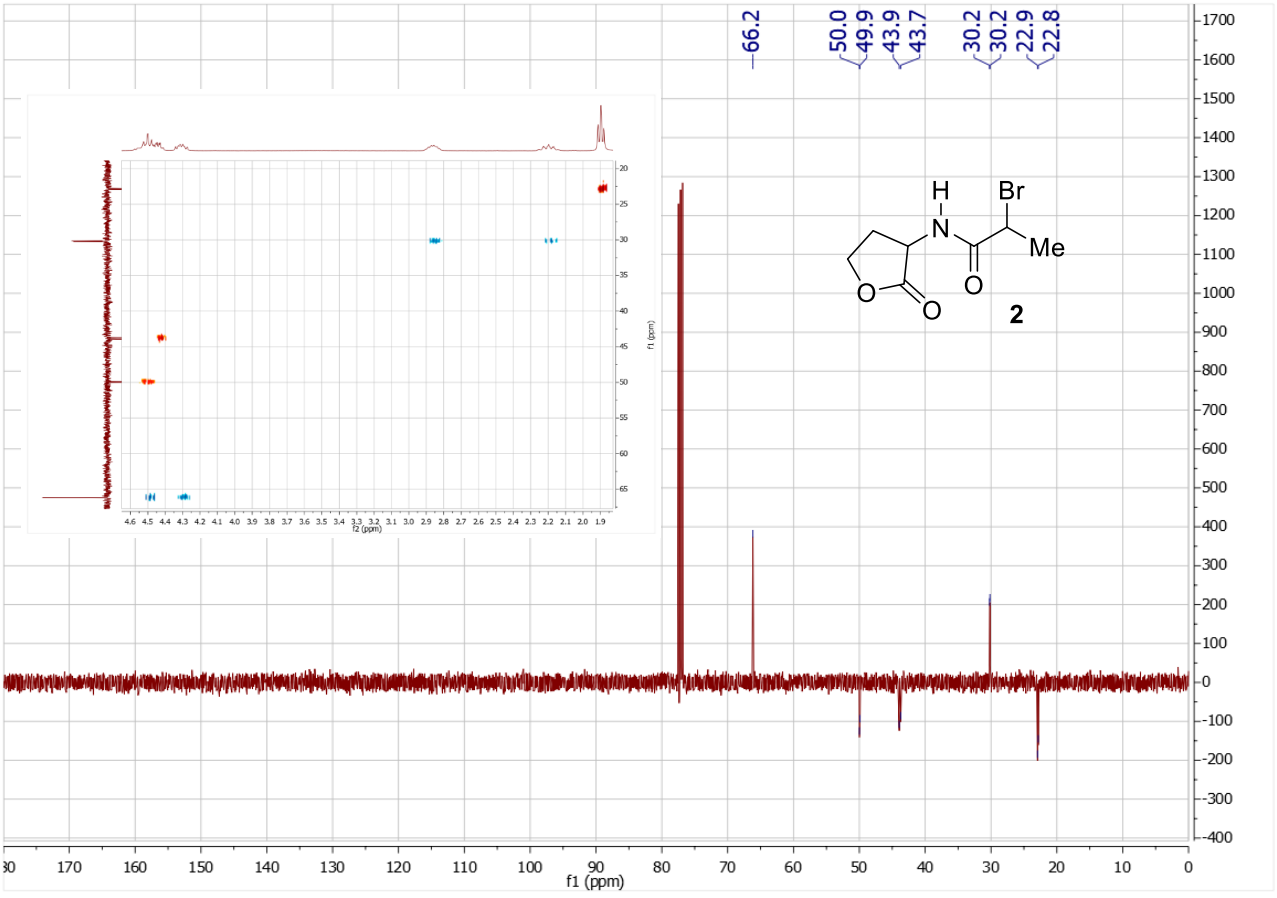
Compound 2: 2-bromo-N-(2-oxotetrahydrofuran-3-yl)propanamide 2



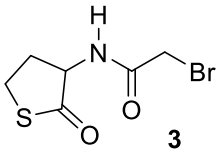
2-bromo-*N*-(2-oxotetrahydrofuran-3-yl)propanamide
Chemical Formula: $C_7H_{10}BrNO_3$
Exact Mass: 234.9844
Molecular Weight: 236.0650

Bromopropionoyl bromide (593 mg, 2.75 mmol, 0.29 mL), α-amino-γ-butyrolactone hydrobromide (500 mg, 2.75 mmol) and triethylamine (556 mg, 5.49 mmol) in chloroform (20 mL). Column chromatography (50% EtOAc in chloroform) gave **2** (215 mg, 0.91 mmol) in 33% yield as a white solid (1:1 mixture of diasteroisomers). δ_H 6.82/6.77 (1H, 2 br s, NH), 4.41-4.58 (3H, m, 3 x CH), 4.27-4.34 (1H, m, CH), 2.83-2.90 (1H, m, CH), 2.14-2.26 (1H, m, CH), 1.89/1.91 (3H, 2 x d, *J* 6.7 Hz, 2 x CH_3); δ_C 66.2, 50.0/49.9, 43.9/43.7, 30.2/30.2, 22.9/22.8 (2 x C not observed); ν_{max} 3284, 3083, 2946, 1775, 1656, 1551, 1165; MS(CI) 236.0 (80%, $[C_7H_{10}{}^{79}BrNO_3+H]^+$) 238.0 (80%, $[C_7H_{10}{}^{81}BrNO_3+H]^+$), 258.0 (100%, $[C_7H_{10}{}^{79}BrNO_3+Na]^+$), 260.0 (98%, $[C_7H_{10}{}^{81}BrNO_3+Na]^+$); HRMS(ES) found 235.9919, $C_7H_{11}{}^{79}BrNO_3{}^+$ ($[M+H]^+$) requires 235.9917.


6.82
6.77
4.58
4.41
4.34
4.27
2.90
2.83
2.26
2.14
1.91
1.90
1.88
H
N
Br
Me
O
O
O
2
0.92
2.98
1.00
1.00
0.98
3.02
f1 (ppm)

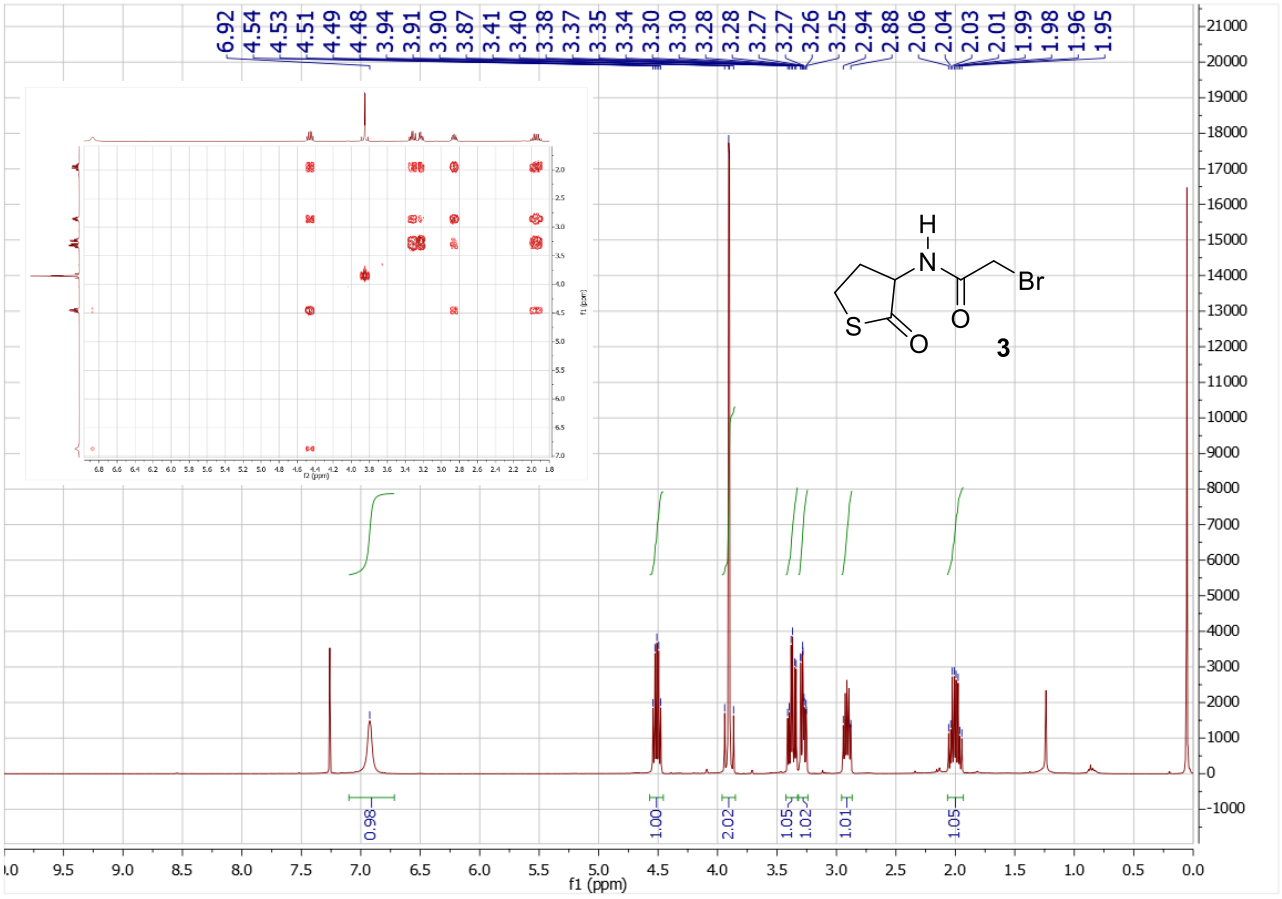

66.2
50.0
49.9
43.9
43.7
30.2
30.2
22.9
22.8
H
N
Br
Me
O
O
O
2
f1 (ppm)

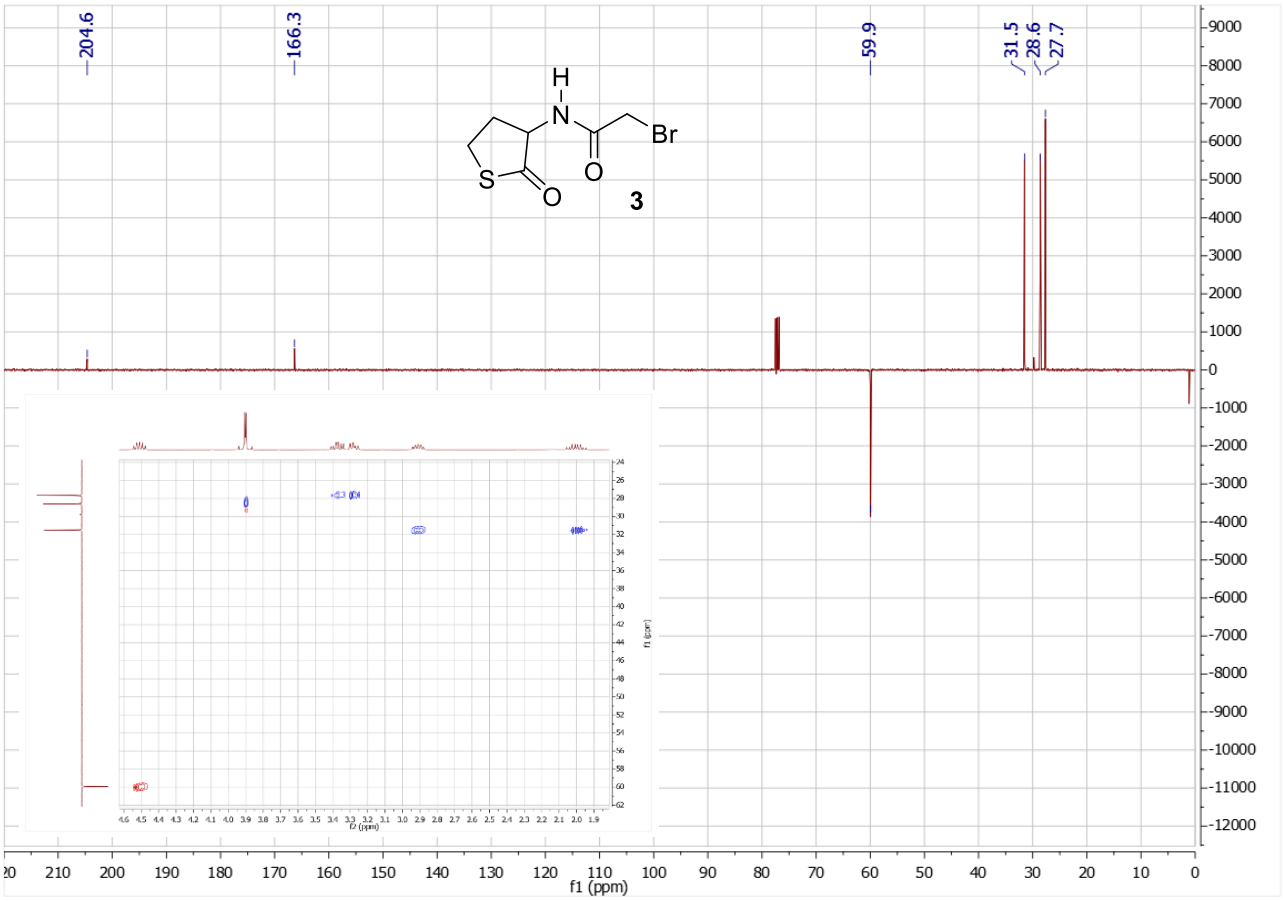
Compound 3: 2-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)acetamide 3



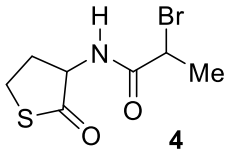
2-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)acetamide
Chemical Formula: $C_6H_8BrNO_2S$
Exact Mass: 236.9459
Molecular Weight: 238.0990

Bromoacetyl bromide (1.31 g, 6.51 mmol, 0.57 mL), homocysteine thiolactone hydrochloride (500 mg, 3.25 mmol), potassium carbonate (1.35 g, 9.76 mmol), water (20 mL), chloroform (20 mL). Column chromatography (50% EA in CF) gave **3** (307 mg, 1.29 mmol) in 40% yield as a white solid. δ_H 6.92 (1H, s, NH), 4.51 (1H, ddd, *J* 6.6, 6.6, 12.4 Hz, CH), 3.93 (1H, d, *J* 13.7 Hz, CH), 3.89 (1H, d, *J* 13.7 Hz, CH), 3.38 (1H, ddd, *J* 5.1, 11.6, 12.0 Hz, CH), 3.23 (1H, ddd, *J* 0.8, 7.0, 12.2 Hz, CH), 2.88-2.94 (1H, m, CH), 2.00 (dddd, *J* 7.0, 12.0, 12.2, 12.4 Hz, CH); δ_C 204.6, 166.3, 59.9, 31.5, 28.6, 27.7; ν_{max} 3262, 1697, 1658, 1537, 1453; MS(CI) 238.0 (95%, $[C_6H_8{}^{79}BrNO_2S+H]^+$) 240.0 (100%, $[C_6H_8{}^{81}BrNO_2S+H]^+$), 260.0 (80%, $[C_6H_8{}^{79}BrNO_2S+Na]^+$), 262.0 (85%, $[C_6H_8{}^{81}BrNO_2S+Na]^+$); HRMS(ES) found 237.9534, $C_6H_9{}^{79}BrNO_2S^+$ ($[M+H]^+$) requires 237.9532.



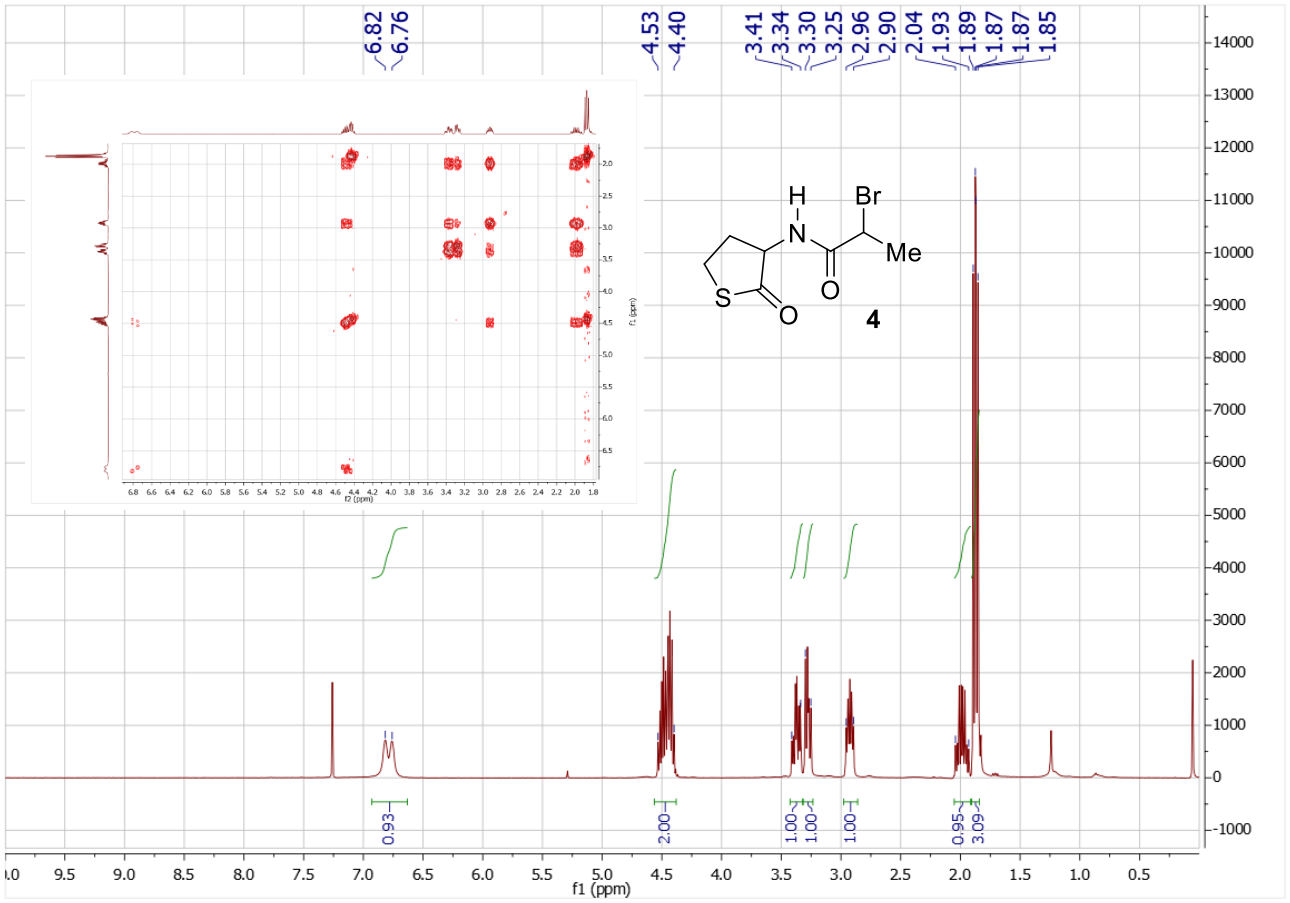


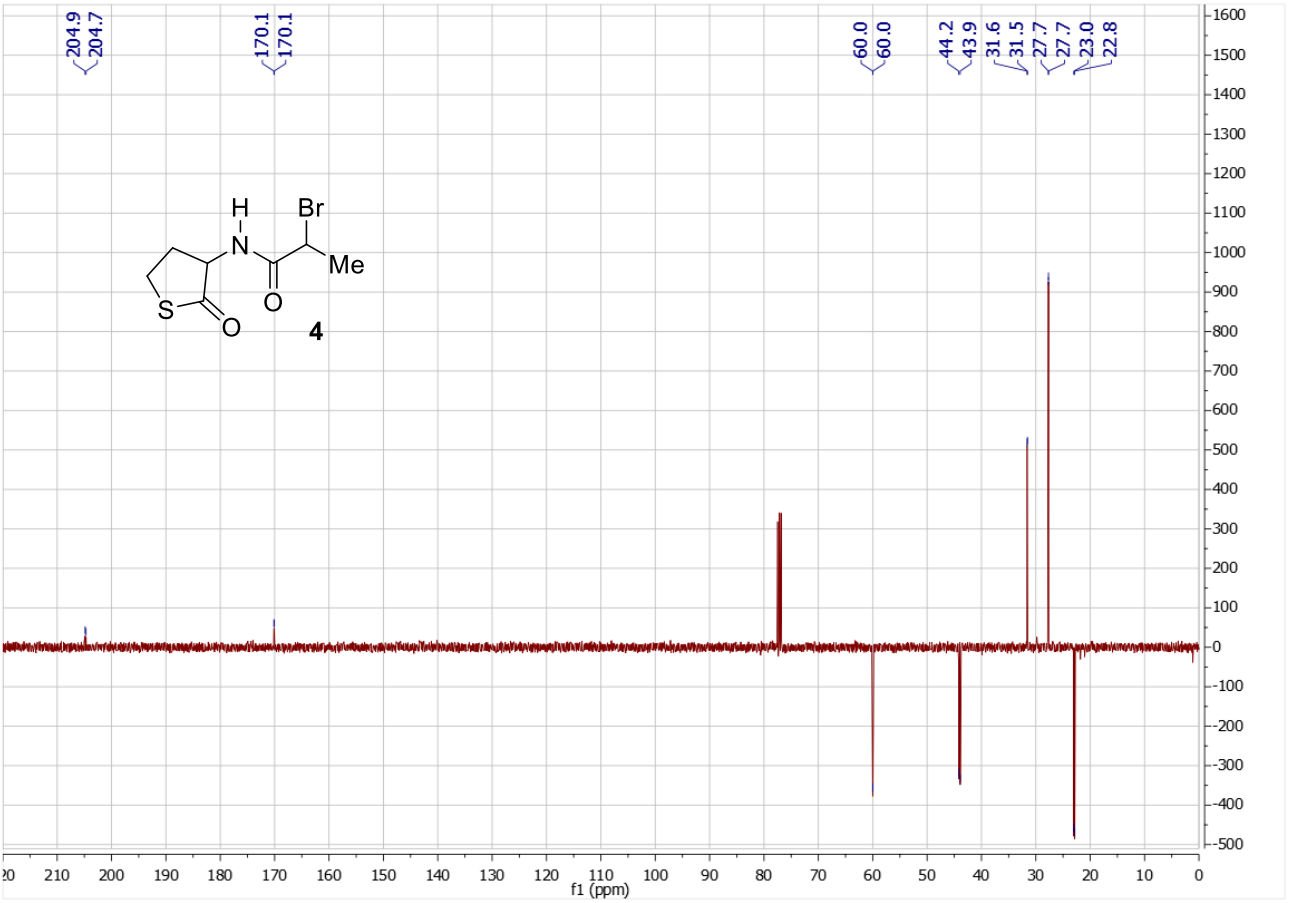
Compound 4: 2-bromo-N-(2-oxotetrahydrothiophen-3-yl)propanamide 4



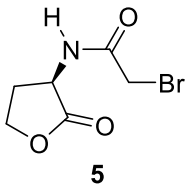
2-bromo-*N*-(2-oxotetrahydrothiophen-3-yl)propanamide
Chemical Formula: $C_7H_{10}BrNO_2S$
Exact Mass: 250.96
Molecular Weight: 252.13

Bromopropionyl bromide (1.41 g, 6.51 mmol, 0.68 mL), homocysteine thiolactone hydrochloride (500 mg, 3.25 mmol), potassium carbonate (1.35 g, 9.76 mmol), water (20 mL), chloroform (20 mL). Column chromatography (50% EtOAc in chloroform) gave **4** (598 mg, 2.37 mmol) in 73% yield as a white solid. δ_H 6.82/6.76 (1H, 2 x br s, 2 x NH), 4.40-4.53 (1H, m, CH), 3.34-3.41 (1H, m, CH), 3.25-3.30 (1H, m, CH), 2.90-2.96 (1H, m, CH), 1.93-2.04 (1H, m, CH), 1.86/1.89 (3H, d/d, *J* 7.0/7.1 Hz, 2 x CH_3); δ_C 204.9/204.7, 170.1/170.1, 60.0/60.0, 44.2/43.9, 31.6/31.5, 27.7/27.7, 23.0/22.8; ν_{max} 3256, 3080, 2970, 1686, 1644, 1553; MS(CI) 252.0 (95%, $[C_7H_{10}{}^{79}BrNO_2S+H]^+$) 254.0 (100%, $[C_7H_{10}{}^{81}BrNO_2S+H]^+$), 269.0 (65%, $[C_7H_{10}{}^{79}BrNO_2S+Na]^+$), 271.0 (65%, $[C_7H_{10}{}^{81}BrNO_2S+Na]^+$); HRMS(ES) found 251.9688, $C_7H_{11}{}^{79}BrNO_2S^+$ ($[M+H]^+$) requires 251.9688.


6.82
6.76
4.53
4.40
3.41
3.34
3.30
3.25
2.96
2.90
2.04
1.93
1.89
1.87
1.87
1.85
H
N
Br
Me
S
O
O
4
0.93
2.00
1.00
1.00
1.00
0.95
3.09
f1 (ppm)


204.9
204.7
170.1
170.1
60.0
60.0
44.2
43.9
31.6
31.5
27.7
27.7
23.0
22.8
H
N
Br
Me
S
O
O
4
f1 (ppm)

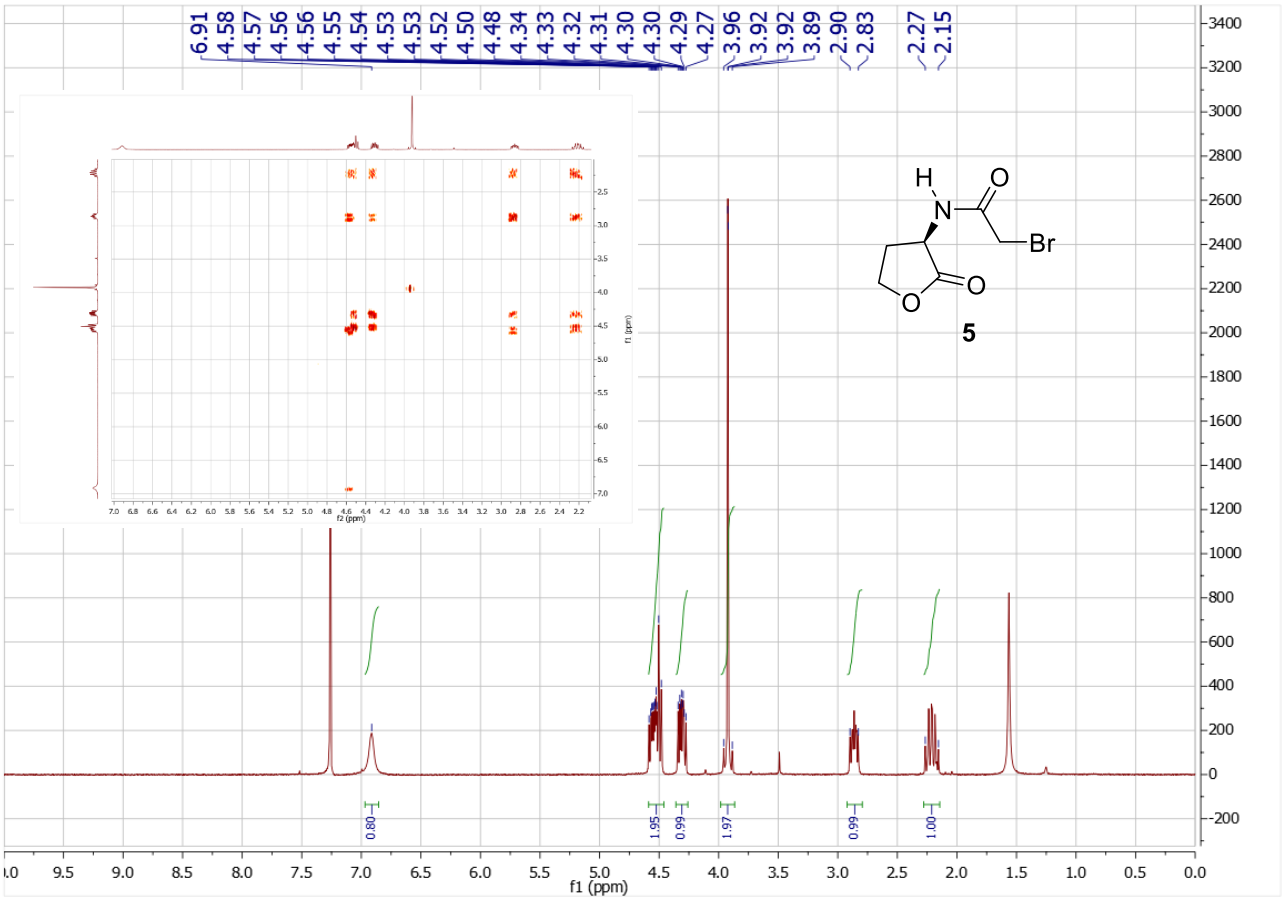
Compound 5: (*R*)-2-bromo-N-(2-oxotetrahydrofuran-3-yl)acetamide 5

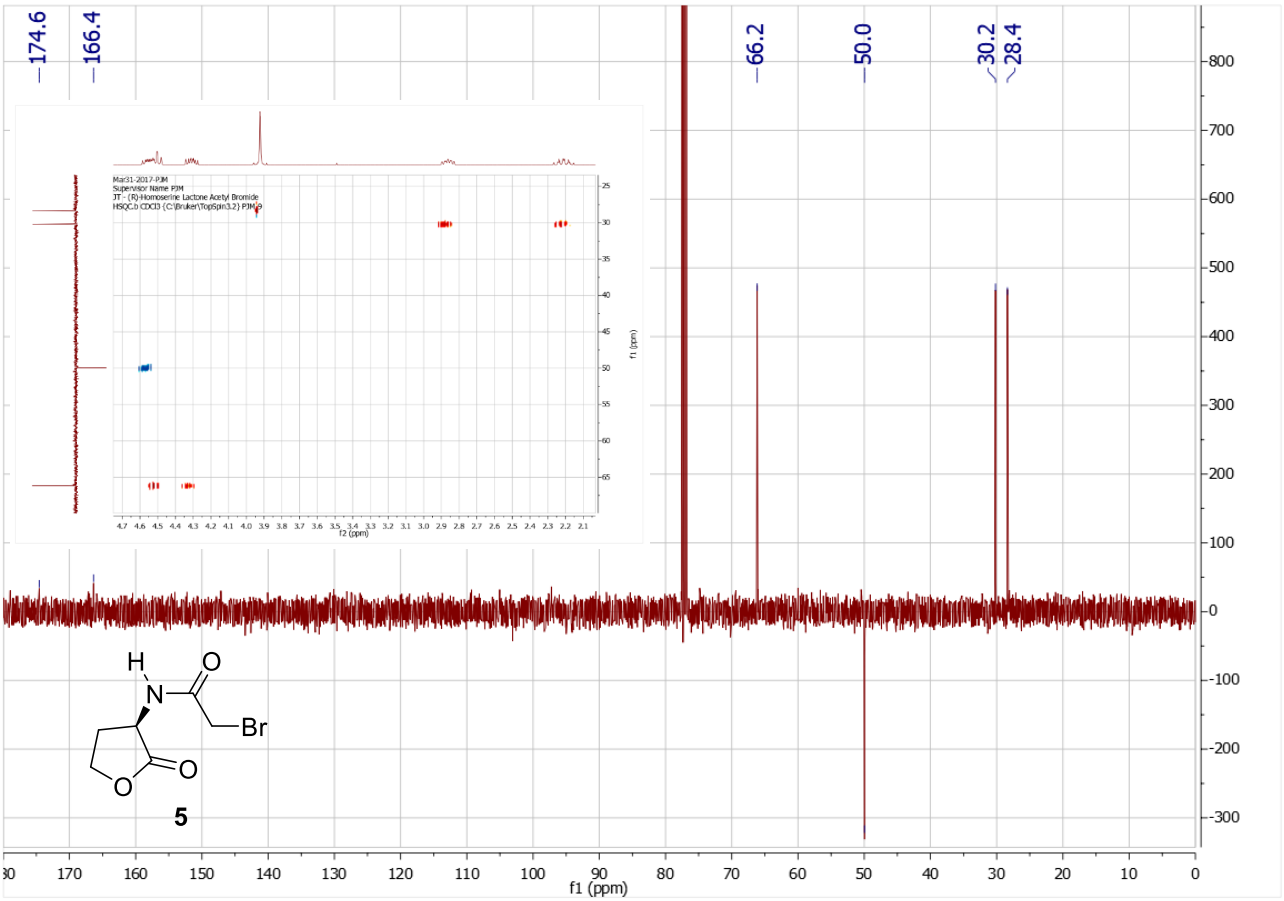


5

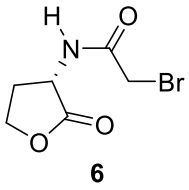
(*R*)-2-bromo-*N*-(2-oxotetrahydrofuran-3-yl)acetamide
Chemical Formula: $C_6H_8BrNO_3$
Exact Mass: 220.9688
Molecular Weight: 222.0380

Bromoacetyl bromide (1.47 g, 7.27 mmol, 0.63 mL), (*R*)-(+)-α-Amino-γ-butyrolactone hydrochloride (500 mg, 3.63 mmol), potassium carbonate (1.51 g, 10.90 mmol), water (20 mL), chloroform (20 mL). column chromatography (50% EA in CF) gave **5** (204 mg, 0.92 mmol) in 25% yield as a white solid. $[\delta]_D^{19}$ -22 (c = 0.1 $CHCl_3$), δ_H 6.91 (1H, br s, NH), 4.55 (1H, ddd, *J* 6.1, 8.6, 11.5 Hz, CH), 4.52 (1H, br t, *J* 8.9 Hz, CH), 4.34 (1H, ddd, *J* 5.9, 9.5, 11.1 Hz), 3.96 (1H, d, *J* 13.7 Hz, CH), 3.92 (1H, d, *J* 13.7 Hz, CH), 2.82-2.90 (1H, m, CH), 2.15-2.26 (1H, m, 1H); δ_C 174.6, 166.4, 66.2, 50.0, 30.2, 28.4; ν_{max} 3253, 3064, 1762, 1657, 1551, 1179; MS(CI) 222.0 (98%, $[C_6H_8{}^{79}BrNO_3+H]^+$) 224.0 (97%, $[C_6H_8{}^{81}BrNO_3+H]^+$), 244.0 (98%, $[C_6H_8{}^{79}BrNO_3+Na]^+$), 246.0 (98%, $[C_6H_8{}^{79}BrNO_3+Na]^+$); HRMS(ES) found 221.9762, $C_6H_9{}^{79}BrNO_3^+$ ($[M+H]^+$) requires 221.9760.



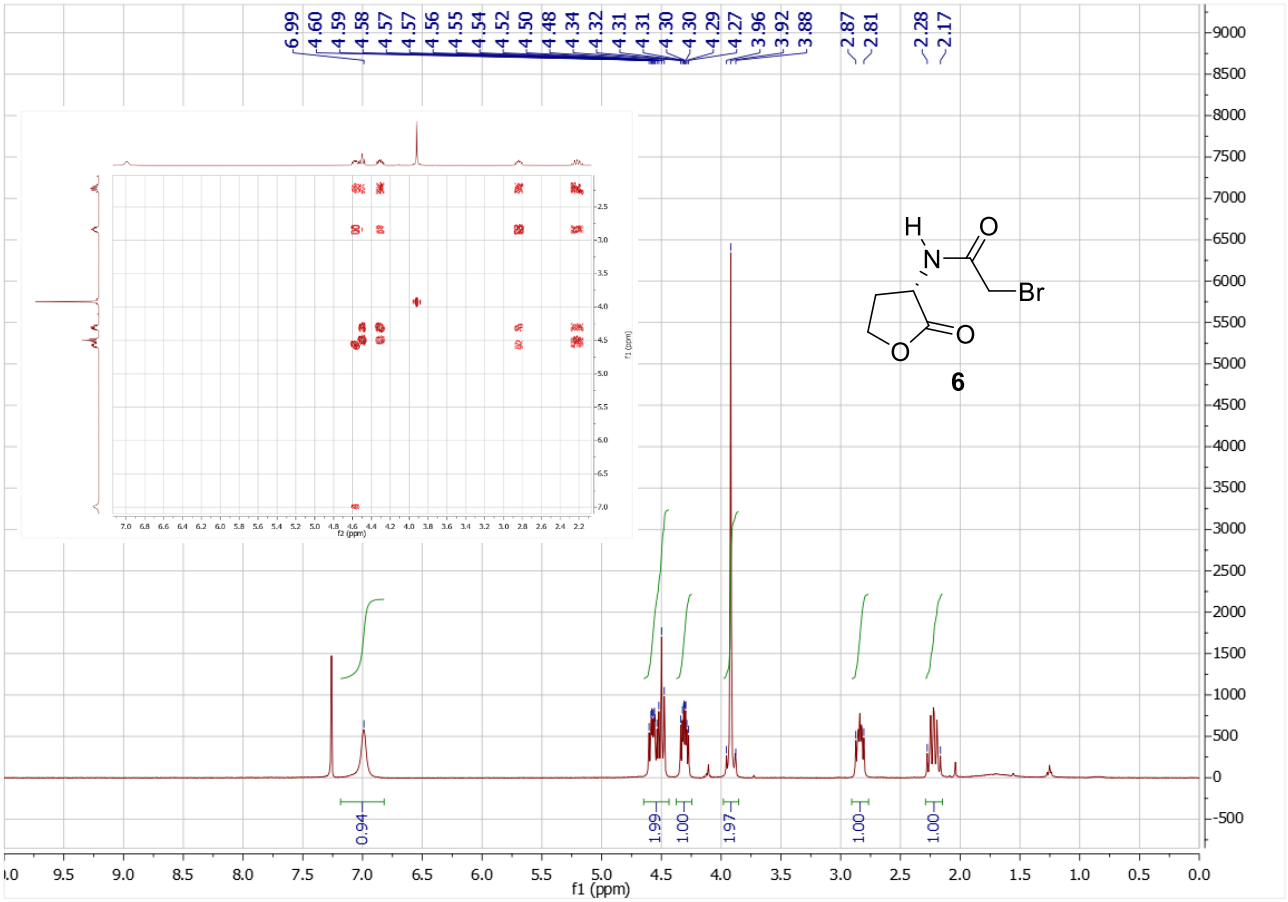


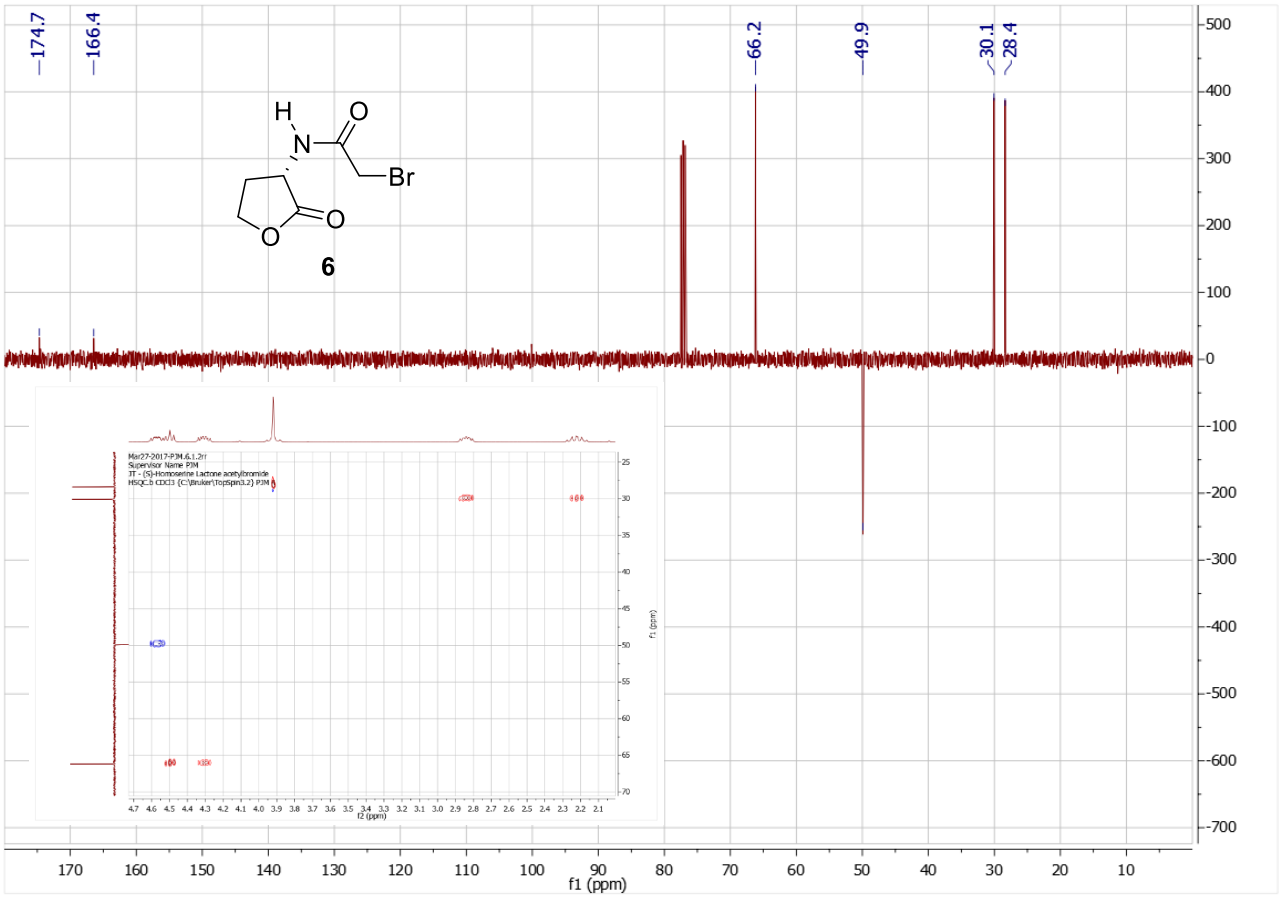
Compound 6: (*S*)-2-bromo-N-(2-oxotetrahydrofuran-3-yl)acetamide 6[13]



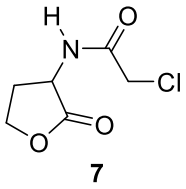
(*S*)-2-bromo-*N*-(2-oxotetrahydrofuran-3-yl)acetamide
Chemical Formula: $C_6H_8BrNO_3$
Exact Mass: 220.9688
Molecular Weight: 222.0380

Bromoacetyl bromide (1.47 g, 7.27 mmol, 0.63 mL), (*S*)-(-)-α-Amino-γ-butyrolactone hydrochloride (500 mg, 3.63 mmol), potassium carbonate (1.35 g, 9.76 mmol), water (20 mL), chloroform (20 mL). Column chromatography (50% EA in CF) gave **6** (116 mg, 0.52 mmol) in 14% yield as a white solid. $[\delta]_D^{19}$ 21 (c = 0.1 $CHCl_3$), Lit.[13] $[\delta]_D^{22}$ 20.5 (c = 0.0074 $CHCl_3$); δ_H 6.99 (1H, s, NH), 4.55 (1H, ddd, *J* 6.1, 8.6, 11.5 Hz, CH), 4.52 (1H, br t, *J* 8.9 Hz, CH), 4.34 (1H, ddd, *J* 5.9, 9.5, 11.1 Hz), 3.96 (1H, d, *J* 13.7 Hz, CH), 3.92 (1H, d, *J* 13.7 Hz, CH), 2.81-2.87 (1H, m, CH), 2.17-2.28 (1H, m, 1H); δ_C 174.7, 166.4, 66.2, 49.9, 30.1, 28.4; ν_{max} 3254, 3065, 1762, 1656, 1551, 1177; MS(CI) 222.0 (100%, $[C_6H_8{}^{79}BrNO_3+H]^+$) 224.0 (98%, $[C_6H_8{}^{81}BrNO_3+H]^+$), 244.0 (85%, $[C_6H_8{}^{79}BrNO_3+Na]^+$), 246.0 (85%, $[C_6H_8{}^{79}BrNO_3+Na]^+$); HRMS(ES) found 221.9761, $C_6H_9{}^{79}BrNO_3{}^+$ ($[M+H]^+$) requires 221.9760.


6.99
4.60
4.59
4.58
4.57
4.57
4.56
4.55
4.54
4.52
4.50
4.48
4.34
4.32
4.31
4.31
4.30
4.30
4.29
4.27
3.96
3.92
3.88
2.87
2.81
2.28
2.17
H
N
O
Br
O
O
6
0.94
1.99
1.00
1.97
1.00
1.00
f1 (ppm)


174.7
166.4
66.2
49.9
30.1
28.4
H
N
O
Br
O
O
6
f1 (ppm)

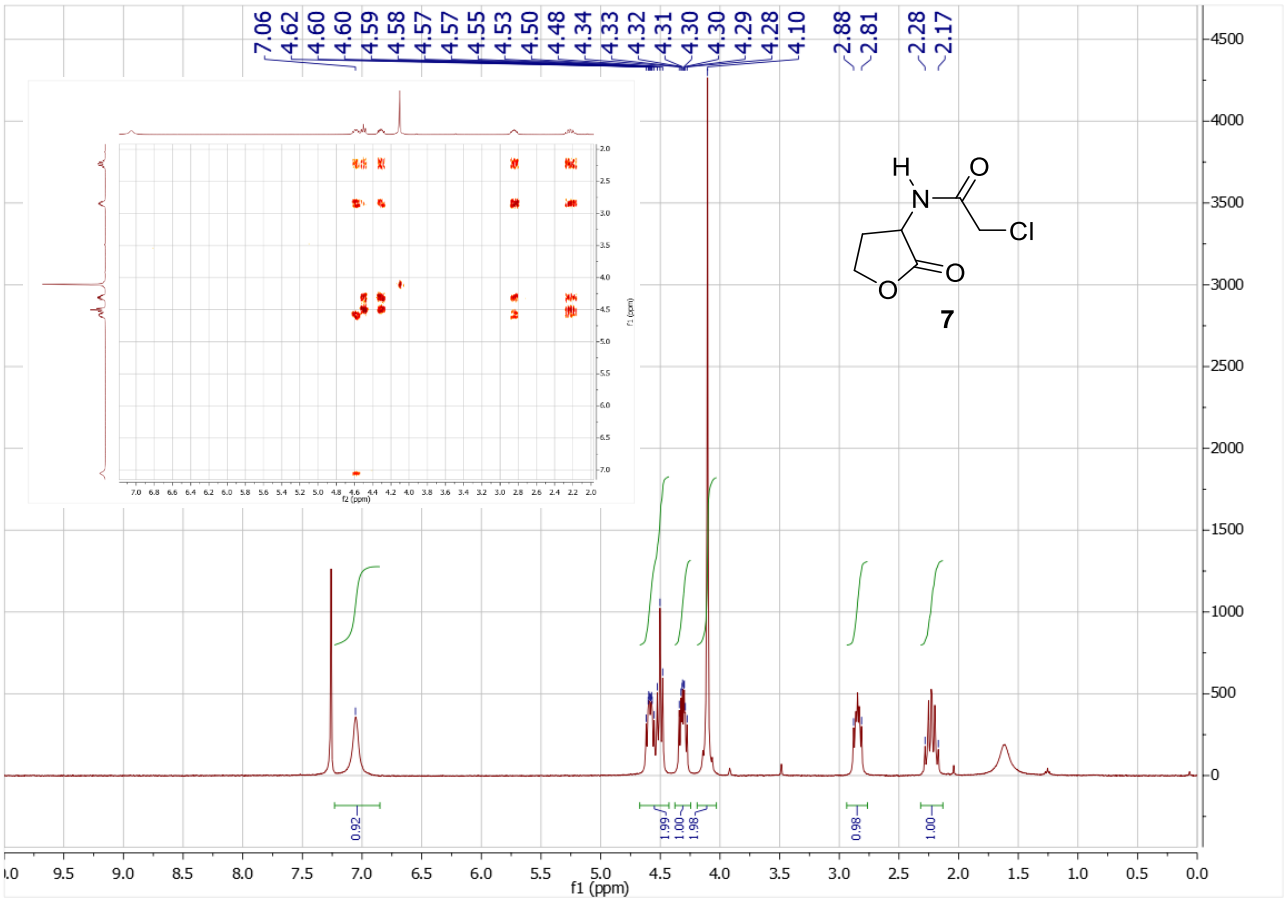
Compound 7: 2-chloro-N-(2-oxotetrahydrofuran-3-yl)acetamide 7

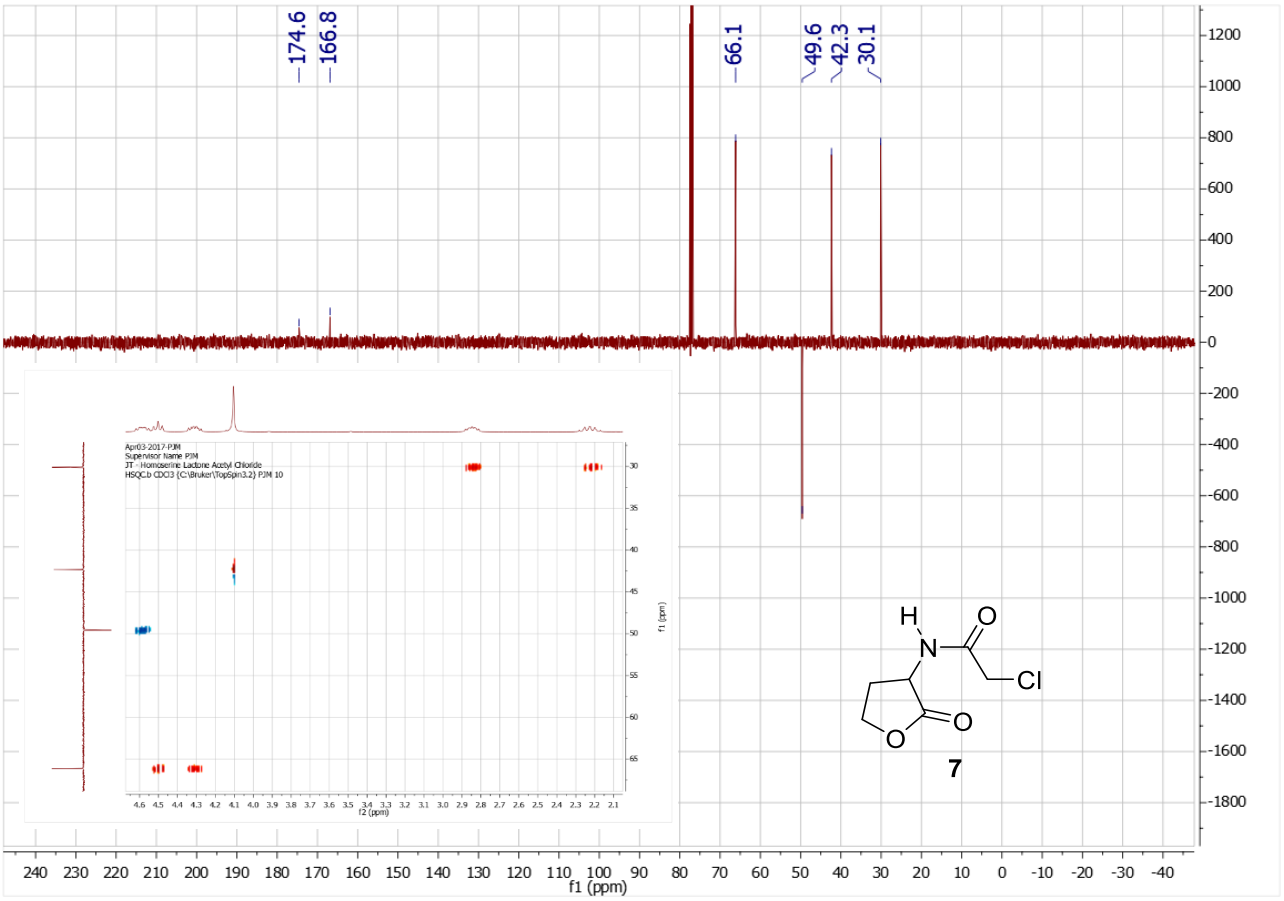


7

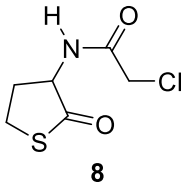
2-chloro-*N*-(2-oxotetrahydrofuran-3-yl)acetamide
Chemical Formula: $C_6H_8ClNO_3$
Exact Mass: 177.0193
Molecular Weight: 177.5840

Chloroacetyl chloride (310 mg, 2.75 mmol, 0.22 mL), α-amino-γ-butyrolactone hydrobromide (500 mg, 2.75 mmol), triethylamine (556 mg, 5.49 mmol), chloroform (20 mL). Column chromatography (50% EtOAc in chloroform) gave **7** (334 mg, 1.88 mmol) in 68% yield as a white solid. δ_H 7.05 (1H, br s, NH), 4.58 (1H, ddd, *J* 6.6, 8.6, 11.4 Hz, CH), 4.50 (1H, br t, *J* 9.0 Hz, CH), 4.31 (1H, ddd, *J* 5.9, 9.7, 10.8 Hz, CH), 4.10 (2H, s, CH_2), 2.81-2.88 (1H, m, CH), 2.17-2.28 (1H, m, 1H); δ_C174.6, 166.8, 66.1, 49.6, 42.3, 30.1; ν_{max} 3251, 3069, 1762, 1662, 1556, 1179, 1024; **MS(CI)** 178.0 (100%, $[C_6H_8{}^{35}ClNO_3+H]^+$) 180.0 (30%, $[C_6H_8{}^{37}ClNO_3+H]^+$), 200.0 (100%, $[C_6H_8{}^{35}ClNO_3+Na]^+$), 202.0 (30%, $[C_6H_8{}^{37}ClNO_3+Na]^+$); HRMS(ES) found 178.0264, $C_6H_9{}^{37}ClNO_3{}^+$ ($[M+H]^+$) requires 178.0265.



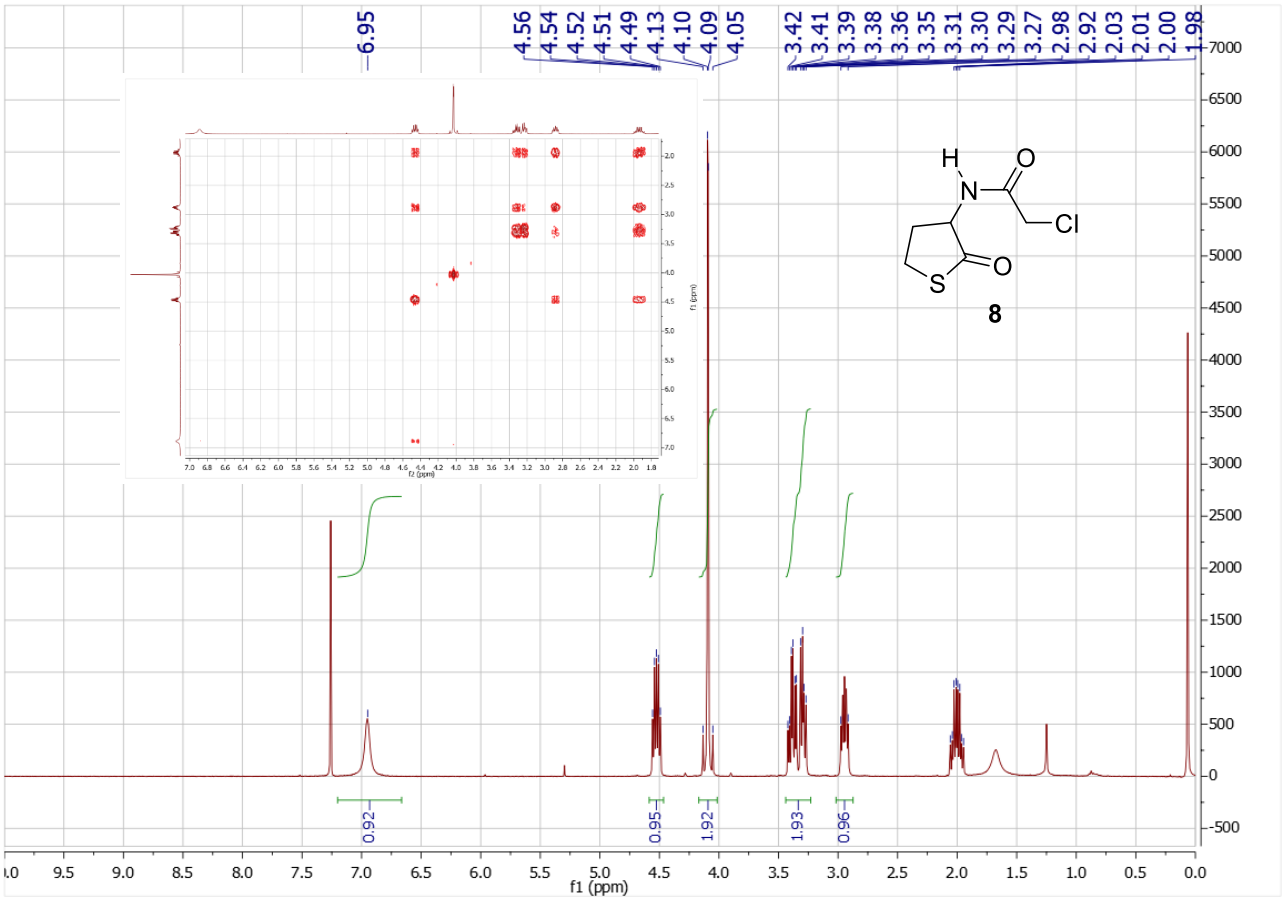


Compound 8: 2-chloro-N-(2-oxotetrahydrothiophen-3-yl)acetamide 8



2-chloro-*N*-(2-oxotetrahydrothiophen-3-yl)acetamide
Chemical Formula: $C_6H_8ClNO_2S$
Exact Mass: 192.9964
Molecular Weight: 193.6450

Chloroacetyl chloride (753 mg, 6.51 mmol, 0.52 mL), homocysteine thiolactone hydrochloride (500 mg, 3.25 mmol), potassium carbonate (1.35 g, 9.76 mmol), water (20 mL), chloroform (20 mL). Column chromatography (50% EA in CF) gave **8** (382 mg, 1.97 mmol) in 61% yield as a white solid. δ_H 6.95 (1H, br s, NH), 4.52 (1H, apparent pentet, 6.5 Hz, CH), 4.12 (1H, d, *J* 15.1 Hz, CH), 4.07 (1H, d, *J* 15.1 Hz, CH), 3.39 (1H, ddd, *J* 5.1, 11.6, 11.6 Hz, CH), 3.29 (1H, br dd, *J* 7.0, 11.2 Hz, 1H), 2.91-2.98 (1H, m, CH), 2.00 (1H, dddd, *J* 7.0, 12.5, 12.5, 12.5 Hz, 1H); δ_C 204.5, 166.7, 59.7, 42.5, 31.7, 27.7; ν_{max} 3293, 2941, 1702, 1643, 1534, 1262; MS(CI) 194.0 (100%, $[C_6H_8{}^{35}ClNO_2S+H]^+$) 196.0 (35%, $[C_6H_8{}^{37}ClNO_2S+H]^+$), 216.0 (65%, $[C_6H_8{}^{35}ClNO_2S+Na]^+$), 218.0 (23%, $[C_6H_8{}^{37}ClNO_2S+Na]^+$); HRMS(ES) found 194.0037, $C_6H_9{}^{35}ClNO_2S^+$ ($[M+H]^+$) requires 194.0037.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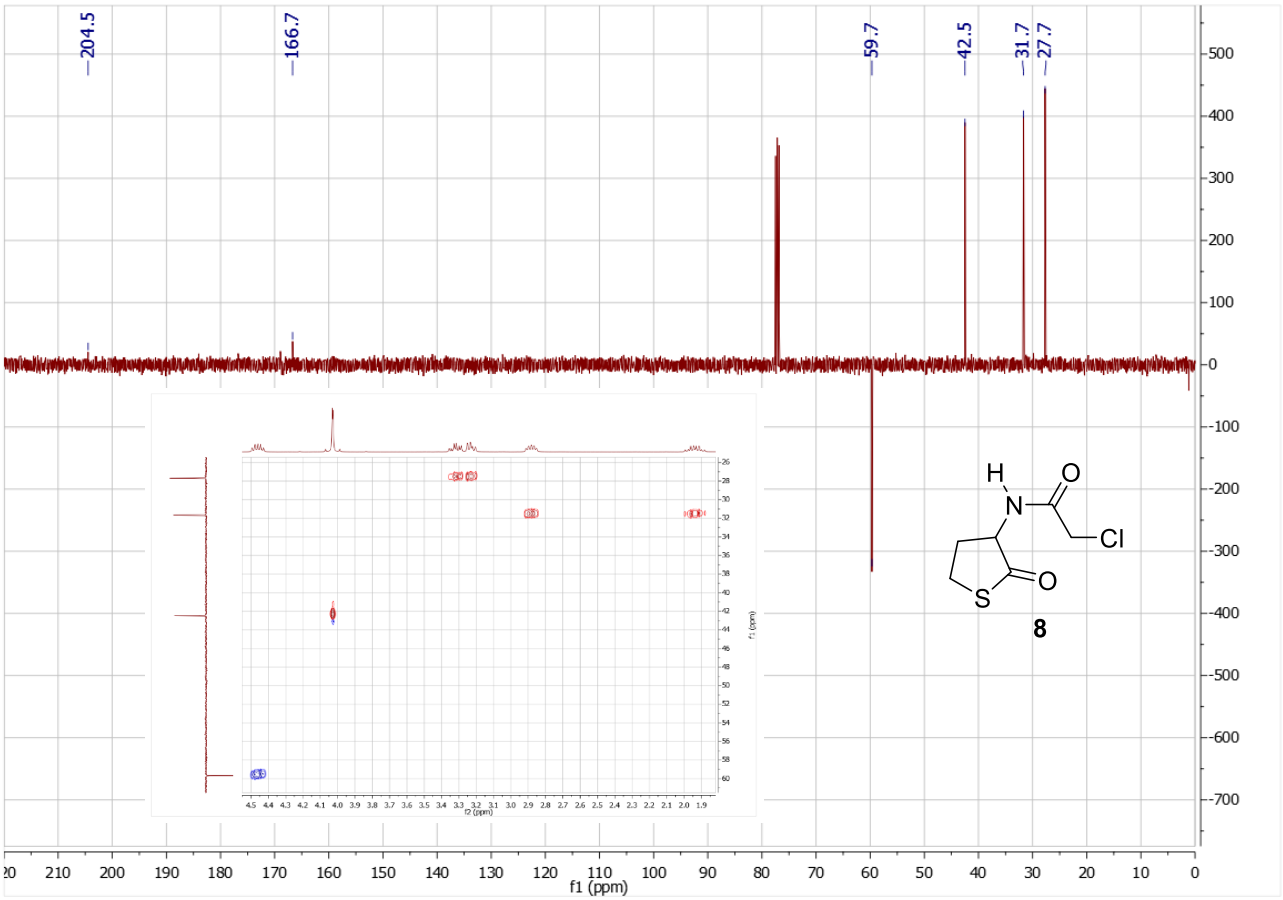
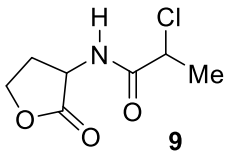
3.38
3.36
3.35
3.31
3.30
3.29
3.27
2.98
2.92
2.03
2.01
2.00
1.98
0.92
0.95
1.92
1.93
0.96
f1 (ppm)
H
N
O
Cl
S
O
8


204.5
166.7
59.7
42.5
31.7
27.7
f1 (ppm)
H
N
O
Cl
S
O
8

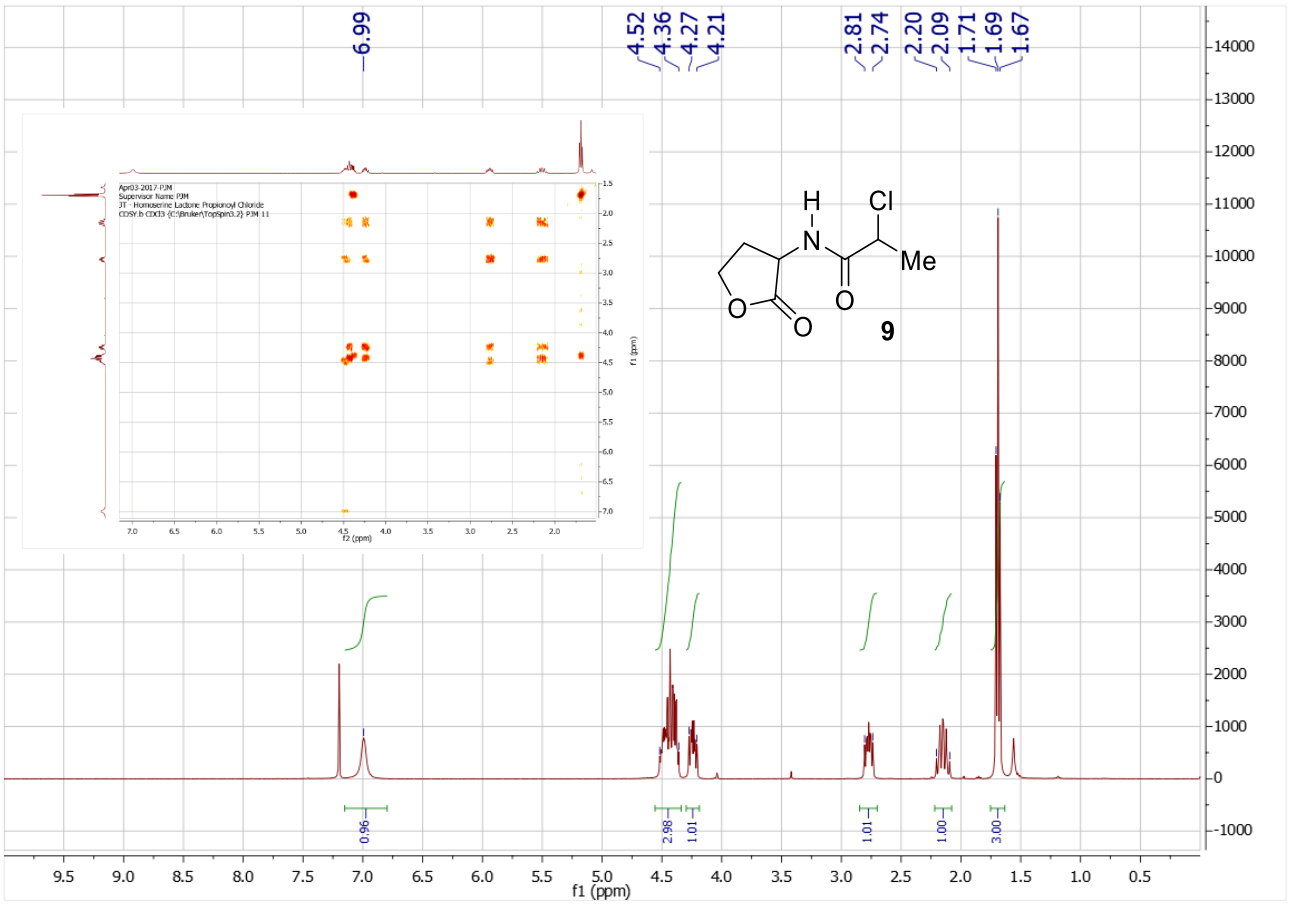
Compound 9: 2-chloro-N-(2-oxotetrahydrofuran-3-yl)propanamide 9

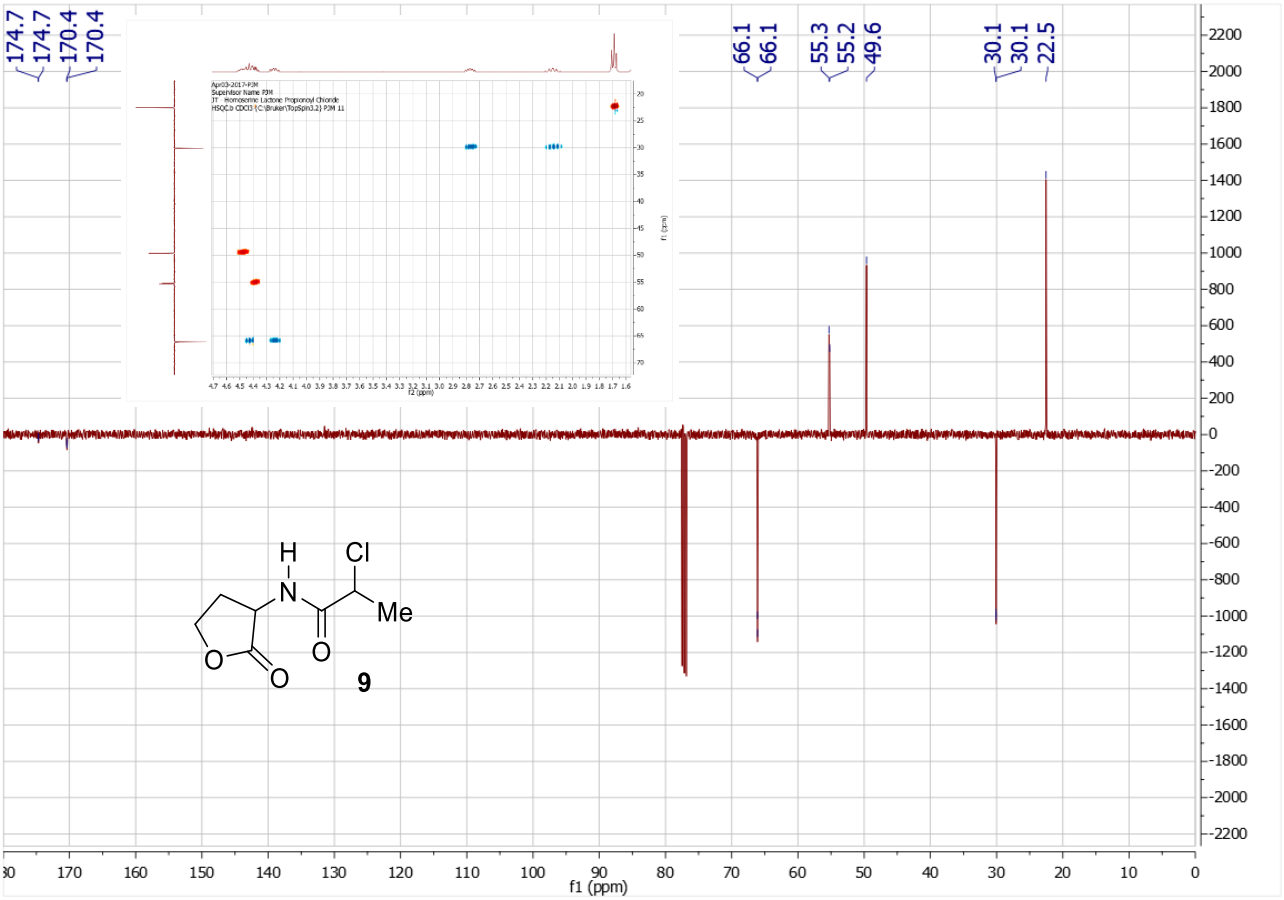


9

2-chloro-*N*-(2-oxotetrahydrofuran-3-yl)propanamide
Chemical Formula: $C_7H_{10}ClNO_3$
Exact Mass: 191.0349
Molecular Weight: 191.6110

Chloropropianoyl chloride (349 mg, 2.75 mmol, 0.27 mL), α-amino-γ-butyrolactone hydrobromide (500 mg, 2.75 mmol) and triethylamine (556 mg, 5.49 mmol), chloroform (20 mL). Column chromatography (50% EtOAc in chloroform) gave **9** (341 mg, 1.78 mmol) in 65% yield as a white solid (1:1 mixture of diastereoisomers). δ_H 6.99 (1H, br s, NH), 4.36-4.52 (3H, m, 3 x CH), 4.21-4.27 (1H, m, CH), 2.74-2.81 (1H, m, CH), 2.09-2.20 (1H, m, CH), 1.70/1.69 (3H, 2 x d, *J* 6.8/6.7 Hz, Me); δ_C 174.7/174.7, 170.4/170.4, 66.1/66.1, 55.3/55.2, 49.6, 30.1/30.1, 22.5; ν_{max} 3285, 3085, 1775, 1660, 1551, 1167; MS(CI) 192.0 (100%, $[C_7H_{10}{}^{35}ClNO_3+H]^+$) 194.0 (35%, $[C_7H_{10}{}^{37}ClNO_3+H]^+$), 214.0 (85%, $[C_7H_{10}{}^{35}ClNO_3+Na]^+$), 216.0 (25%, $[C_7H_{10}{}^{37}ClNO_3+Na]^+$); HRMS(ES) found 192.0422, $C_7H_{11}{}^{79}ClNO_3{}^+$ ($[M+H]^+$) requires 192.0422.

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170.4
66.1
66.1
55.3
55.2
49.6
30.1
30.1
22.5
H
N
Cl
Me
O
O
O
9
f1 (ppm)